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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,362	01/19/2001	Solomon S. Steiner	PDC 119	8907

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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/766,362	STEINER ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-12,14-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-12,14-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Request for Continued Examination (RCE) under 37 C.F.R. 1.114, the Amendment and Applicant's Arguments/Remarks, all filed 09/25/07 is acknowledged.

Examiner also acknowledges Applicant's statement indicating that the rejection of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 under 35 U.S.C. §103(a) as being obvious over Steiner et al. (USPN 5,503,852) was affirmed by the Board of Patent Appeals and Interferences (decision filed 07/25/07). Applicant's statement that the rejection of claims 3, 8, 10, 16, 20 and 21 under 35 U.S.C. §103(a) as being obvious over Steiner et al. (U.S. Pat. No. 5,503,852) in view of Illum (USPN 5,690,954) as being affirmed by the Board of Patent Appeals and Interferences is also acknowledged.

Claims 1-5, 7-12, 14-18, 20 and 21 are pending in this action. Claims 1, 5, 7, 14 and 18 have been amended. Claims 6, 13 and19 have previously been cancelled. Claims 1-5, 7-12, 14-18, 20 and 21 are rejected.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the

fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 09/25/07 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (hereafter "Steiner") (US Pat. No. 5,503,852).

The instant invention is drawn to a composition, a drug delivery device and method of administering a drug for nasal administration of a drug in a dry powder form suitable for

administration to the nasal region, the dry powder comprising microparticles having a particle size of 10 microns to 20 microns in diameter and comprising the drug and a diketopiperazine.

Steiner *et al.* ('852) teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and Abstract.

According to Steiner, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner *et al.* teach a system based upon diketopiperazine or one of its substitution derivatives, including *diketomorpholines and diketodioxanes*. The diketopiperazine synthetic intermediates are preferably formed by cyclodimerization to form diketopiperazine derivatives at elevated temperatures under dehydrating conditions, functionalized on the side chains, and then precipitated with drug to be incorporated into microparticles (see abstract; col. 4, lines 49-67; col. 7, lines 8-11).

The protective material, the diketopiperazines, are not biologically active and do not alter the pharmacologic properties of the therapeutic agents (col. 11, lines 1-3).

The instant invention is drawn to a composition for the nasal administration of a drug in dry powder form for administration to the nasal region, whereby the dry powder comprises

microparticles having a particle size of 10 to 20 microns and comprising drug and a diketopiperazine. There is no significant patentable distinction observed between the instant invention and the prior art since the prior art teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are between 0.1 to 10 microns in diameter and are used for nasal applications. Steiner explicitly teaches that their microparticles can be between 0.1 and 10 microns. Thus, the '10 micron' size microparticles disclosed by Steiner overlaps with the "10 microns" claimed herein by Applicant and hence the "10 microns" of Steiner satisfies the claim limitation requirement of "10 to 20 microns". The 10 microns taught by the prior art is an overlapping particle size that falls within the range of "10 to 20 microns" instantly claimed and thus reads on the instant particle size limitations. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). In this case, Applicants have not established that their claimed range provides for unexpected results over the ranges disclosed by the art.

Furthermore, Applicants have not demonstrated that the "10 micron" size range claimed is a critical lower limit. This is evidenced by Applicant's own specification. For instance, formulations I and II on pages 13 and 14 demonstrate particles with micron sizes that are less than 10 microns. More specifically, formulation I on p. 13 demonstrates that 10% of particles had a particle size of only *3.15* microns. Similarly, Formulation II on page 14 demonstrates that 10% of particles had a particle size of only *2.99* microns. Therefore, this clearly establishes that the 'between 10 microns' claimed by Applicants is not a critical lower maximum particle size

limitation. The determination of a suitable or effective particle size is within the level of one of ordinary skill in the art, based on routine experimentation. In this instance, one of ordinary skill in the art would have been motivated to nasally administer the microparticles of Steiner that comprise a drug and diketopiperazine and further optimize, if necessary, the particle size or size range for the intended application (i.e., nasal applications). One would be motivated to do this with a reasonable expectation of success of obtaining an enhanced drug delivery system that effectively (nasally) administers the microparticles in the (nasal) cavity for maximum treatment. It is the position of the Examiner that the 10-micron size microparticles of Steiner would be retained in the mucosal cavity for sufficient drug delivery and thus, would be suitable for their intended purpose. Absent a showing of evidence to the contrary, Steiner's microparticles would be suitable for nasal administration. Hence, the instant invention, given the explicit teachings of Steiner delineated above, would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

* * * * *

Claims 3, 8, 10, 16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steiner *et al.* (US Pat. No. 5,503,852) as applied to claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 above and further in view of Illum (US Pat. No. 5,690,954).

Steiner *et al.* ('852), as delineated above, teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be

delivered and are between 0.1 to 10 microns in diameter and whereby the microparticles are used for diagnostic applications for imaging of the nasal tract (see reference col. 4, lines 30-55); (col. 10, lines 25-49); (col. 13, lines 13-24) and abstract.

According to Steiner, biologically active agents having therapeutic, prophylactic or diagnostic activities can be delivered and include active agents, such as hormones, vasoactive agents, anesthetics or sedatives, steroids, decongestants, antivirals, antisense, antigens, antibodies and the like (col. 10, lines 25-49).

Steiner does not explicitly teach the selective antihistamines chosen from chlorpheniramine and azelastine.

Illum ('954) teaches a drug delivery system for nasal administration of an active drug in dry powder form wherein the drug delivery system comprises microsphere particles formed of active drugs that include *antihistamines*, vasoconstrictors, anti-inflammatory agents and anesthetics whereby the composition is administered in the form of a dry powder having a particle size of from about 10 microns to about 100 microns (see reference column 5, line 14 through col. 6, line 53); (col. 9, lines 24-61). (The range of about 10 microns to about 100 microns taught by Illum encompasses the range of "10 to 20 microns" claimed by Applicant).

Suitable active drugs disclosed are anti-inflammatory agents, vasoconstrictors, anesthetics (analgesics) and antihistaminic agents. Antihistaminic agents are diphenhydramine hydrochloride, *chloropheniramine maleate* and clemastine. The microspheres are administered via the nasal route using a nasal insufflator device. Examples of these are already employed for

commercial powder systems intended for nasal application (*e.g.*, Fisons Lomudal System); (col. 8, line 44 through col. 9, line 60).

Illum teaches that the drug to be administered to a mucosal surface such as the nose, eye, etc., can be administered as a powder and can also be administered in the form of a colloidal particle comprising a microsphere system (col. 5, line 14-26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the antihistamines (*i.e.*, chlorpheniramine) as taught by Illum within the microparticulate formulations of Steiner. One would be motivated to do so with a reasonable expectation of success because Illum teaches a nasally administered drug delivery system and device comprising active agents that include antistamines, such as those claimed, as well as vasoconstrictors and anesthetics (analgesics), which are effective active agents for their formulation and teach that the drugs are used for nasal administration provided in a dry powder form. The expected result would be an improved and effective microparticulate drug delivery system for nasal administration, as also desired by Applicant.

Pertinent Art

Prior Art made of record and deemed relevant by Examiner:

U.S. Patent No. 6,136,835 Camden 10/2000

Response to Arguments

Applicant's arguments filed 09/25/07 have been fully considered but were not found to be persuasive.

- **Rejection under 35 U.S.C. §103(a) of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 over Steiner et al. (US Pat. No. 5,503,852)**:

Applicant argued, "Steiner discloses several drug delivery systems using dikeopiperazines and their analogs to form microparticles encapsulating drug to be delivered. The microparticles may be microspheres with diameters ranging between 0.1 and 10 microns. Steiner does not disclose drug delivery systems for nasal administration. While Steiner does mention that the microparticles can include a diagnostic imaging agent useful for imaging the nasal tract, the microparticles are administered orally or through a needle for intravenous inhalation. The particles are administered in a solution or in the form of a tablet, not in a dry powder. None of the forms are suitable for nasal administration. Steiner does not mention microparticles having a size of 10 microns to 20 microns. The size range taught by Steiner (from 0.1 to 10 microns) is ineffective for improving nasal administration of drugs."

These arguments have been fully considered but were not found to be persuasive. The instant claims are drawn to a composition for nasal administration of a drug in a dry powder form suitable for administration to the nasal region, the dry powder form comprising microparticles having a particle size of 10 to 20 microns and comprising the drug and a diketopiperazine. Steiner et al. teach drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine, wherein the microparticles are formed in the presence of the drug to be delivered. The microparticles are used for diagnostic applications for imaging of the *nasal tract* and Steiner et al. teach that microparticles that bind to mucosal membranes are particularly preferred (see col. 13, lines 13-21). It is the position of the Examiner that the microparticles of

Steiner would be retained in the mucosal cavity for sufficient drug delivery based on their micron size and thus, would be suitable for their intended purpose. Absent a showing of evidence to the contrary, Steiner's microparticles would be suitable for nasal administration. Regarding particle size, the particle size taught by Steiner is between 0.1 to 10 microns in diameter. Applicants claim a particle size of 10 to 20 microns. The '10 micron' size microparticles disclosed by Steiner amply overlaps with the "10 microns" claimed herein by Applicant. Hence the "10 microns" of Steiner sufficiently satisfies the claim limitation requirement of "10 to 20 microns". The 10 microns taught by the prior art is an overlapping particle size that falls within the range of "10 to 20 microns" instantly claimed and thus reads on the instant particle size limitations. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). In this case, Applicants have not established that their claimed range provides for unexpected results over the ranges disclosed by the art.

Furthermore, Applicants have not demonstrated that the "10 micron" size range claimed is a critical lower limit. This is evidenced by Applicant's own specification. For instance, formulations I and II on pages 13 and 14 demonstrate particles with micron sizes that are less than 10 microns. More specifically, formulation I on p. 13 demonstrates that 10% of particles had a particle size of only *3.15* microns. Similarly, Formulation II on page 14 demonstrates that 10% of particles had a particle size of only *2.99* microns. Therefore, this clearly establishes that the "10-20 microns" claimed by Applicant is not a critical lower particle size limitation.

Applicant argues, "Steiner does not provide the necessary motivation to modify its particles so that they are suitable for nasal administration." This argument was not persuasive since, based on Steiner's teachings, one of ordinary skill in the art would have been motivated to nasally administer Steiner's microspheres comprising a drug and diketopiperazine and further optimize, if necessary, the particle size or size range for the intended application (i.e., nasal applications). One would be motivated to do this with a reasonable expectation of success of obtaining an enhanced drug delivery system that effectively (nasally) administers the microparticles in the (nasal) cavity for maximum treatment. It remains the position of the Examiner that the 10-micron size microparticles of Steiner, which directly overlaps with the "10 microns" claimed by Applicant, would be retained and sufficiently bind to the mucosal cavity for sufficient drug delivery and thus, would be suitable for the intended purpose.

- **Rejection under 35 U.S.C. §103(a) of claims 3, 8, 10, 16, 20 and 21 over Steiner et al. (USPN 5,503,852) in view of Illum (USPN 5,690,954):**

Applicant argued, "Illum does not disclose the inclusion of a dikeopiperazine in the delivery system."

This argument was not persuasive since Steiner initially teaches drug delivery systems based on the formation of diketopiperazine microparticles and microencapsulation of drugs by derivatives of diketopiperazine. Illum was relied upon for the teaching of the selective antihistamines claimed, such as chlorpheniramine and was not relied upon for the teaching of the inclusion of diketopiperazine, as argued herein by Applicant. Illum further teaches microspheres that can be administered via the nasal route using a nasal insufflator device (col. 9, lines 53-54).

Applicant argued, "Neither Steiner nor Illum provide a person of ordinary skill in the art with the motivation to combine these references. Steiner discloses delivery of small microparticles, which are not suitable for nasal administratoni in a dry powder form. Steiner's microparticles have diameters ranging from 0.1 to 10 microns. In contrast, Illum is directed to particles with larger diameters, raning from 10 to 100 microns, which may be administered to the nasal mucosa for drug delivery."

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, ample motivation has been supplied by the prior art to arrive at the instant invention. Steiner's microparticles, taught to be from 0.1 to 10 microns, would be suitable for nasal administration. The microparticles of Steiner are used for diagnostic applications for imaging of the *nasal tract* and Steiner et al. teach that microparticles that bind to mucosal membranes are particularly preferred (see col. 13, lines 13-21). It should be noted that the "10 microns" size taught by Steiner effectively overlaps with the "10 microns" claimed by Applicant. Illum teaches particles administered to the nasal mucosa, ranging from 10 to 100 microns. Here also, as is the case with Steiner, the "10 microns" taught by Illum sufficiently meet the "10 microns" claimed by Applicant. Even further, the "10 to 100 microns" microparticle range disclosed by Illum clearly encompasses the "10 to 20 microns" instantly claimed. Thus, both Steiner and Illum teach relatively small particle sizes that either overlap with the claimed range (Steiner) or encompass the claimed range (Illum) (see also page 15 of the BPAI decision).

Applicant argued, "Illum discloses a broad range of diameters for the particles and does not teach particles having a narrow size range of 10 to 20 microns, as required by the amended claims. Illum discloses that microsphere delivery systems for nasal mucosa must both have bioadhesive properties and contain absorption enhancers to increase bioavailability of the drug to be delivered. Applicants have found a different delivery system, one which merely requires the use of diketopiperazine and does not require formation of a gel or addition of absorption enhancers."

This argument was not persuasive since the range disclosed by Illum (10 to 100 microns), which although broad, nonetheless encompasses the range being claimed by Applicant (10 to 20 microns). Thus, the prior art range, albeit, broader than the instant range, does in fact encompass the instant narrower range.

The argument that "Illum's microsphere must have bioadhesive properties and contain absorption enhancers" was not persuasive because the instant "comprising" claim language permits the presence of additional components asides from those recited, including the gel-forming materials and absorption enhancers of Illum. The additional components disclosed by Illum are not excluded based on the instant "comprising" claim language.

Applicant argued, "Neither Steiner nor Illum disclose forming microparticles by spray drying. Illum discloses forming microspheres by emulsion and phase separation methods. Steiner discloses microparticles via precipitation. Therefore, the combination of Steiner with Illum would not make claims 20 and 21 obvious."

This argument was not persuasive since spray drying methods are well known in the art, as evidenced by Applicants themselves (see specification page 3, last ¶). Claims 20 and 21 would have be obvious to one of ordinary skill in the art based on the teachings of Steiner and Illum, in view of Applicant's admission regarding spray drying methods.

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday during regular business hours. (Wednesdays - Telework).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Art Unit 1615

November 10, 2007

HUMERA N SHEIKH
PRIMARY EXAMINER

hns